Effects of Hyper-Early (<12 Hours) Endovascular Treatment of Ruptured Intracranial Aneurysms on Clinical Outcome

A. CONSOLI[1], G. GRAZZINI[2], L. RENIERI[1], A. ROSI[2], A. DE RENZIS[2], C. VIGNOLI[2], S. NAPPINI[1], F. AMMANNATI[3], L. CAPACCIOLI[2], S. MANGIAFICO[1]

[1] *Interventional Neuroradiology Unit,* [2] *Department of Radiology,* [3] *Department of Neurosurgery I, Careggi University Hospital; Florence, Italy*

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Summary

Despite the encouraging results obtained with the endovascular treatment of ruptured intracranial aneurysms, few data are available on the effects of the timing of this approach on clinical outcome. The aim of our study was to evaluate the effects of the hyper-early timing of treatment and of pre-treatment and treatment-related variables on the clinical outcome of patients with ruptured intracranial aneurysms.

Five hundred and ten patients (167 M, 343 F; mean age 56.45 years) with 557 ruptured intracranial aneurysms were treated at our institution from 2000 to 2011 immediately after their admission. The total population was divided into three groups: patients treated within 12 hours (hyper-early, group A), between 12-48 hours (early, group B) and after 48 hours (delayed, group C). A statistical analysis was carried out for global population and subgroups.

Two hundred and thirty-four patients (46%) were included in group A, 172 (34%) in group B and 104 (20%) in group C. Pre-treatment variables (Hunt&Hess, Fisher grades, older age) and procedure-related variable (ischaemic/haemorrhagic complications) showed a significant correlation with worse clinical outcomes. The hyper-early treatment showed no correlation with good clinical outcomes. The incidence of intraprocedural complications was not significantly different between the three groups; 1.2% of pre-treatment rebleedings were observed.

The hyper-early endovascular treatment of ruptured intracranial aneurysm does not seem to be statistically correlated with good clinical outcomes although it may reduce the incidence of pre-treatment spontaneous rebleedings without being associated with a higher risk of intraprocedural complications. However, since no significant differences in terms of clinical outcome and pre-treatment rebleeding rate were observed, a hyper-early treatment is not be supported by our data.

Introduction

Subarachnoid haemorrhage (SAH) secondary to the rupture of saccular intracranial aneurysms may be treated with both surgical and endovascular approaches. The ISAT study [1] provided most of the available information regarding the indications, type of treatment and the intermediate and long-term clinical outcome. This multicentre randomized controlled trial compared the effectiveness and the mid to long-term clinical outcome of surgical and endovascular approaches, concluding that patients treated with endovascular coiling had a significantly better clinical outcome at one year follow-up than the surgical group and similar outcomes after five years [2]. Although these results encouraged the endovascular treatment of ruptured intracranial aneurysms, few studies have focused on the critical issues of this approach such as the timing of treatment and the differences between interventional techniques, and almost all of them referred to surgical series [3-8]. Furthermore, a prospective study on a group of patients with ruptured aneurysms treated with surgical clipping demonstrated that early treatment may reduce the risk of rebleeding [9]. However, the effects of timing on safety and effectiveness of endovascular treatment of ruptured intracranial aneurysms have rarely been considered. Baltsavias et al. [10] showed that the latency between the onset of symptoms and endovascular treatment did not influence the morbidity rate and the clinical outcome after six months, while the surgical approach should be performed as early as possible to reduce the risk of vasospasm that is correlated to poor outcomes. The aim of this retrospective study was to evaluate the effects of timing on the effectiveness and safety of endovascular treatment in patients with ruptured intracranial aneurysms.

Materials and Methods

Five hundred and thirty consecutive patients with 557 ruptured intracranial aneurysms underwent endovascular treatment at our institution from January 2000 to January 2011. Seven patients with dissecting and blister-like aneurysms, one patient admitted for rebleeding after surgical treatment and 13 unsuccessful treatments (one was attempted in a patient with a dissecting aneurysm) secondary to difficult vascular access and instability of the guiding catheter because of arterial tortuosity were excluded. In case of multiple aneurysms more than one was treated during the same procedure when it was not possible to determine the offending lesion. Finally, the study cohort included 510 patients with 537 aneurysms (167 males, 343 females; mean age 56.45 years, range: 14 – 86 years). All patients were admitted after a CT scan was positive for SAH that was assessed with Fisher's classification [11], while Hunt&Hess scale [12] was used for clinical evaluation. The neurosurgeon and interventional neuroradiologist evaluated each case together to choose the modality of treatment: embolization was considered the first-line treatment except in those cases in which the evacuation of the haematoma was mandatory or arterial branches originated from the aneurysmal sac and, therefore, a surgical approach was preferred. About 40% of the patients (195/510, 38.2%) were referred to our institution from peripheral hospitals and this may explain most of the delayed treatments that also included misdiagnosed cases and could justify different intervals between the onset of symptoms and access to the Emergency Department. All the patients were treated immediately after admission and only in nine cases was the treatment postponed because of the unavailability of the angiographic suite at the time of the patient's arrival. The endovascular procedures were performed under general anaesthesia, systemic heparinization and monitoring of activated clotting time values. Nimodipine was administered after the procedure to prevent vasospasm. After the procedure 20 patients underwent surgical evacuation of an intracerebral haematoma when it determined worsening evolution of the mass effect and an external ventricular drainage was positioned in 58 patients. Three hundred and two patients were treated with simple coiling, 207 with the remodelling technique and only in one case was stent-assisted coiling performed. The grade of occlusion was assessed with DSA evaluation using Raymond's classification [13] and clinical outcome at discharge and after six months was evaluated by clinical examination and telephonic interviews, using the modified Rankin Scale [14] (mRS). The study population was divided into three groups (Table 1): patients treated within 12 hours from the onset of symptoms (group A, hyper-early treatment), between 12-48 hours (group B, early treatment) and after 48 hours (group C, delayed treatment). H&H and Fisher grade at admission, grade of occlusion at the end of the procedure and after six months, periprocedural complications, clinical outcome at discharge and after six months, morbidity and mortality rates were evaluated considering the entire population and separate groups. Two neuroradiologists with 20 years' and ten years' experience retrospectively and separately reviewed all the cases and the angiographic follow-up examinations. Chi square test, logistic regression and Mantel-Haenszel test for linear association were used to perform uni- and multivariate analysis within the three different groups, k value was used to assess inter-observer agreement. Variables that showed p values >0.05 in univariate analysis were not included in the multivariate analysis. SPSS software version 19 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Results

We report only the data regarding the entire study population while the findings observed within separate groups are summarized in Table 1. The inter-observer agreement revealed k=0.82 (Table 2).

Angiographic findings and clinical outcome in the study population

At the end of the procedure 449 aneurysms were completely obliterated (grade I Raymond's classification, 83.6%), a residual neck (grade II) and a sac remnant (grade III) were

Table 1 **Subgroups**

	A					B					C				
N° of patients	234					17 2					104				
Gender															
M	80					48					40				
F	154					12 4					64				
HH	*1*	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*
	15	70	53	43	53	1 7	73	44	21	17	3 9	42	9	11	3
Fisher	*1*	*2*	*3*	*4*		*1*	*2*	*3*	*4*		*1*	*2*	*3*	*4*	
	7	42	73	112		1 0	59	58	45		2 5	39	15	25	
Location	*S*	*M*	*L*	*G*	*Total*	*S*	*M*	*L*	*G*	*Total*	*S*	*M*	*L*	*G*	*Total*
ICA	18	31	17	1	67	2 2	34	5	1	62	1 5	16	3	2	36
ACA	11	2	0	0	13	9	2	1	0	12	1	2	0	0	3
ACoA	51	57	5	1	114	3 8	27	3	0	68	2 6	20	0	0	46
MCA	15	5	6	0	26	8	8	2	0	18	4	6	1	1	12
SCA	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
PCA	2	1	1	0	4	3	0	0	1	4	4	1	0	0	5
BA	5	4	1	0	10	1	7	2	0	10	1	2	0	0	3
VA	1	0	0	0	1	1	2	0	0	3	0	0	0	0	0
PICA	6	3	0	0	9	5	2	0	0	7	3	0	0	0	3
Total					245					184					108
Complications															
Thromboembolism			10	4.27%				5	2.90%				5	4.80%	
Perforation			25	10.68%				16	9.30%				10	9.61%	
Mortality Overall per group			41	17.5%				21	12.2%				5	4.8%	
Ischaemia-related			4	0.8%				2	1.1%				0	0,00%	
Perforation-related			9	3.8%				4	2.3%				1	1,00%	
Morbidity Overall per group			27	11.5%				23	13.3%				12	11.5%	
(mRS3-5) Ischaemia-related			3	1.2%				2	1.1%				2	2,00%	
Perforation-related			13	5.5%				7	4%				1	1,00%	
Grade of occlusion at discharge															
I			208	88.9%				153	89.0%				88	84.6%	
II			24	10.2%				21	12.2%				15	14.4%	
III			13	5.6%				10	5.8%				5	4.8%	
Grade of occlusion after 6m															
I			110	47.0%				88	51.2%				44	42.3%	
II			18	7.7%				17	9.9%				21	20.2%	
III			22	9.4%				11	6.4%				10	9.6%	

HH: *Hunt&Hess grade;* ICA: *internal carotid artery*; ACA: *anterior cerebral artery*; ACoA: *anterior communicating artery*; MCA: *middle cerebral artery*; SCA: *superior cerebellar artery*; PCA: *posterior cerebral artery*; BA: *basilar artery*; VA: *vertebral artery*; PICA: *postero-inferior cerebellar artery*; S: *small*, M: *medium*; L: *large*; G: *giant*.

Table 2 **Statistical analysis**

Outcome at discharge					Outcome at 6 months			
Variables	**Test**	**Sign. (p=)**	**Sign. (p=)**		**Test**	**Sign. (p=)**	**Sign. (p=)**	
Pre-treatment		*Univariate*	*Multivariate*			*Univariate*	*Multivariate*	
HH	Pearson χ^2	< 0.001	< 0.001		Pearson χ^2	0.003	< 0.001	
Fisher	Pearson χ^2	< 0.001	< 0.001		Pearson χ^2	0.005	< 0.001	
Age	Pearson χ^2	0.007	0.003		Pearson χ^2	0.007	0.003	
Localization	Pearson χ^2	0.259	n.e.		Pearson χ^2	0.075	n.v.	
Timing (<12h)	Pearson χ^2	0.138	n.e.					
Timing (<12h)	Mantel-Haenszel	0.001	inversecor-relation					
Procedure-related		*Univariate*	*Multivariate*			*Univariate*	*Multivariate*	
Complications	Pearson χ^2	< 0.001	< 0.001	(OR:7.142)	Pearson χ^2	< 0.001	< 0.001	(OR:7.813)
Grade of occlusion	Pearson χ^2	0.002	0.012		Pearson χ^2	0.068	0.012	
Excluding HH4-5		**Univariate**	**Multivariate**					
HH	Pearson χ^2	0.005	0.028					
Fisher	Pearson χ^2	0.006	0.02					
Age	Pearson χ^2	0.143	n.e.					
Localization	Pearson χ^2	0.110	n.e.					
Timing (<12 h)	Pearson χ^2	0.29	n.e.					
Complications	Pearson χ^2	< 0.001	< 0.001	(OR:7.006)				
Grade of occlusion	Pearson χ^2	0.096	n.e.					
Timing < 24 h		**Univariate**	**Multivariate**					
HH	Pearson χ^2	< 0.001	0.038					
Fisher	Pearson χ^2	< 0.001	0.001					
Age	Pearson χ^2	0.141	n.e.					
Location	Pearson χ^2	0.259	n.e.					
Timing (<24 h)	Pearson χ^2	0.003	0.678					
Complications	Pearson χ^2	< 0.001	< 0.001	(OR: 8.603)				
Grade of occlusion	Pearson χ^2	0.002	0.035					
Inter-observer agreement		k=0.82						

Sign.: significativity; *OR:* odds ratio; *HH:* Hunt&Hess grade; *n.e.:* not evaluated.

observed respectively in 60 (11.1%) and 28 cases (5.3%). At discharge 335 patients (65.7%) had no or minimal neurological deficits (mRS0-1), 46 (9.0%) revealed moderate deficits (mRS2-3), 62 (12.1%) a severe disability (mRS4-5) and 67 (13.1%) died (Figure 1A). After six months, excluding deceased patients (67), 342/443 patients (77.2%) were classified as mRS0-1, 42/443 (9.5%) as mRS2-3, 40/443 (9.0%) as mRS4-5, 16 patients (3.5%) had died and three patients (0.7%) could no longer be contacted. Therefore, after six months, 83 patients with 85 aneurysms were deceased (16.2%), 77 patients with 80 aneurysms (15.1%) did not undergo a radiological follow-up because of the poor outcome at discharge (39 patients mRS4-5 with 41 aneurysms) or they were too old (34 patients with 34 aneurysms >75 years were controlled with MR angiography) or too young (one patient with one aneurysm aged 14 years underwent MR angiography control) and three patients with four aneurysms refused further controls. Furthermore, we had no DSA controls for 31 patients with 31 aneurysms because they could no longer be contacted (6.1%). Finally, after six months 242/341 aneurysms (70.9%) were classified as grade I, 56/341 as grade II (16.4%), 43/341 as grade III (12.6%).

Peri-procedural complications

Seventy-six peri-procedural adverse events occurred in 510 cases (76/510, 14.9%). Thromboembolic complications were observed in 20 patients (20/510; 3.9%): seven patients (7/510; 1.3%) had no or minimal deficits at discharge (mRS0-1), seven (1.3%) had a moderate-severe disability (mRS3-5) and six died (6/510; 1.1%). In 55 cases an intra-operative rupture of the sac occurred (55/510; 10.7%): 20 (20/510; 3.9%) patients were discharged as mRS0-1, ten (10/510;

1.9%) had moderate neurological deficits (mRS2-3), 11 (11/510; 2.1%) had a severe disability (mRS4-5) and 14 (14/510; 2.7%) died. Considering the total number of aneurysms (557) intra-operative rupture of the sac was observed in 11% (28/245) in group A, in 8.6% (16/184) in group B and in 10.1% in group C (11/108). In one case a retroperitoneal haematoma (one case, mRS4) was observed. In 45% (33/73) of the cases complications occurred in patients with HH grades 4-5. Furthermore, six spontaneous rebleedings (6/510, 1.2%) were observed before the endovascular treatment (3/245, 1.2% in group A; 3/184, 1.6%, in group B). Overall procedure-related mortality and morbidity were respectively 3.9% (20/510) and 5.4% (28/510). Mortality and morbidity were 1.2% (6/510) and 1.4% (7/510) for ischaemic events and 2.7% (14/510) and 4% (21/510) for haemorrhagic complications.

Discussion

Although endovascular treatment is currently considered a first-line approach for ruptured aneurysms [15], some issues have not yet been clearly established, such as the indication for surgical or endovascular treatment and the effects of timing of aneurysm embolization. Our aim was to investigate which factors may be related to a good clinical outcome after the endovascular treatment of ruptured intracranial aneurysms and, overall, whether the hyper-early treatment could be considered one of these factors.

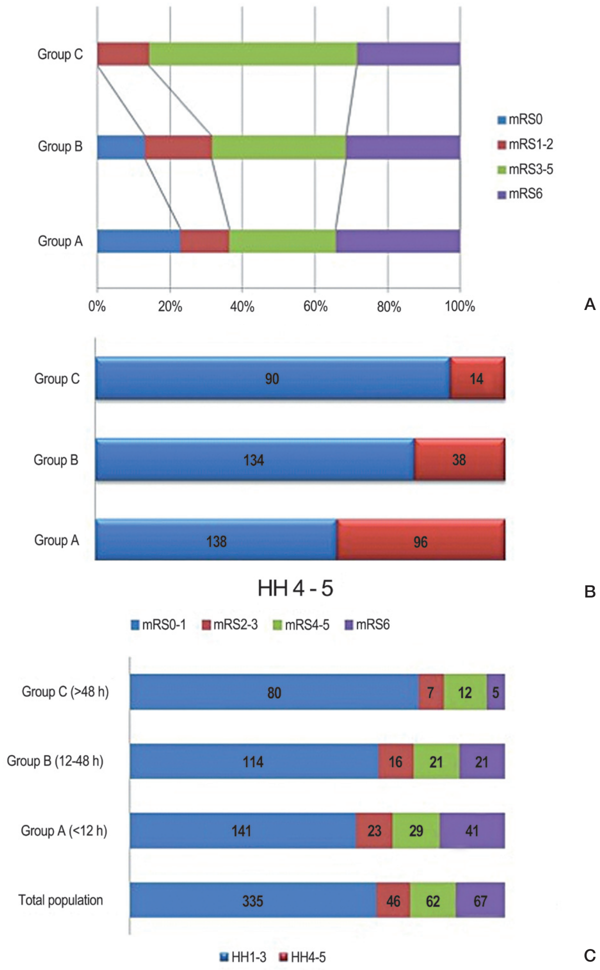

Figure 1 A) Clinical outcomes at discharge. B) The number of patients admitted in a severe clinical condition (Hunt & Hess grades 4-5) and their distribution within the three groups. C) Clinical outcomes at discharge of patients admitted with Hunt&Hess grades 4-5.

Timing of treatment

In our series, hyper-early timing (<12 hours) of the neuro-interventional procedure was not significantly related to a good clinical outcome in the univariate analysis (χ^2; p= 0.138) and seemed to show an inverse correlation with a good clinical outcome (χ^2 for trend; p=0.001). These data might be explained by our tendency, in the last decade, to treat all critical patients as early as possible (Figure 1B), and the outcome could probably depend on their clinical condition rather than the timing of the endovascular treatment (Figure 1C). Furthermore, we also considered and recently agreed with the current opinion about patients admitted in a poor clinical condition (HH4-5): some authors suggested a conservative treatment in intensive care units immediately after admission, considering endovascular or surgical treatment only in case of a clinical improvement [16-18]. Therefore, since that could determine a bias in our study population, we carried out a further statistical analysis excluding patients with a severe clinical condition at admission (HH4-5 and/or Fisher grade 3-4) in order to focus on those patients with minimal or moderate deficits. However, data obtained with this sub-analysis confirmed that a good clinical outcome (mRS≤2) is not significantly associated with the timing of the endovascular treatment (p=0.29). In literature, different timing groups were considered to define early and ultra-early treatment. Baltsavias et al. [10] studied two groups treated respectively before (early treatment) and after 48 hours, concluding that patients should be treated as early as possible without considering the latency between the onset of symptoms and the time of arrival at the hospital, since the early approach (<48 hours) did not increase the periprocedural morbidity and reduced the risk of pre-treatment rebleeding. Philips et al. [19] divided their study population into patients treated before (ultra-early treatment) and after (early treatment) 24 hours and observed that the ultra-early approach (within 24 hours) was significantly related to a better outcome at six months. Although in our experience the concept of early treatment is anticipated, we performed a statistical analysis considering, in our total population, the same groups proposed by Philips et al. Also in our series the endovascular treatment performed within 24 hours showed a significant correlation with a good outcome at discharge and after six months (Pearson χ^2 test; p=0.003) in univariate analysis, but not in the multivariate analysis (Pearson χ^2 test, p=0.678) (Table 2).

Pre-treatment clinical condition

The data obtained with univariate analysis suggest that older age (Pearson χ^2; p=0.007), Hunt&Hess grade (Pearson χ^2; p<0.001) and Fisher grade (Pearson χ^2; p<0.001) were significantly correlated with a worse clinical outcome (Table 2). Also in multivariate analysis these variables maintained a strong relation with a good clinical outcome at discharge and after six months, suggesting that the pre-treatment clinical picture is probably the most influential factor on clinical outcome (HH1-3, Fisher grade 1-2 showed a strong correlation with a good outcome; respectively Pearson χ^2; p=0.005 and p=0.006). Furthermore, the localization of the aneurysmal sac was not significantly correlated to a good clinical outcome either in the total population (Pearson χ^2; p=0.259) or excluding patients classified as HH4-HH5 (Pearson χ^2; p=0.075) (Table 2).

Spontaneous rebleedings before treatment

We experienced only six pre-treatment rebleedings, all within 24 hours, which is a lower rate (6/510; 1.2%) compared with the data reported in surgical series described in the literature [20-29] ranging between 4.1 and 17.3% with high mortality rates (65-80%). In our series 376 patients were treated within 24 hours (73.7%) and 234 of them (234/376; 62.2%) within 12 hours.

Treatment-related variables

The grade of occlusion at the end of the procedure showed a significant correlation with a good clinical outcome in univariate and multivariate analysis considering the global population (respectively Pearson χ^2; p=0.002 and p=0.012), but not excluding HH4-5 patients (Pearson χ^2; p= 0.096) (Table 2). This datum may explain the importance of a total occlusion of the sac in relation to reducing the risk of early rebleeding after endovascular treatment, even if this could not be considered the only factor influencing the good clinical outcome, and the early rebleeding rate in totally or subtotally occluded aneurysms is not well established. However, intra-procedural complications were significantly correlated with a worse outcome both within the global population (Pearson χ^2; p<0.001; OR: 7.142; 95% C.I.) and excluding critical patients (Pearson χ^2; p<0.001; OR: 8.2; 95% C.I.) (Table 2), although no differences were observed between the three groups in terms of the incidence of intra-procedural ischaemic or haemorrhagic complications (14.9% in group A, 12.2% in group B, 14.4% in group C). Furthermore, focusing on procedure-related haemorrhagic events, no differences were observed considering patients treated within and after 24 hours (respectively 39/376, 10%, and 12/134, 9%). The fragility of the aneurysmal sac, which may predispose to a higher risk of spontaneous or procedure-related haemorrhagic events, seems to be quite similar in the three groups: in group A pre-embolization rebleedings or intra-procedural ruptures occurred in 12% (31/245), in group B in 10.3% (19/184) and in group C in 10.1% (11/108). These data support previous experiences reported in literature, even if a different timing for endovascular treatment was considered (before and after 48 hours) [10,30]. The main limit of this study is that it is a retrospective series and the timing of endovascular treatment could not be randomized. However, this study may reflect a real scenario in which the timing of the treatment depends on factors such as the tendency of these patients to under or overestimate headache (especially in those cases in which it is the only symptom), the capability of general practitioners or doctors working in

Emergency Departments to suspect a SAH and the transport from a peripheral hospital.

Conclusions

The pre-treatment clinical picture (HH and Fisher grade), the grade of occlusion and the incidence of intra-procedural complications are significantly correlated with the clinical outcome of patients with ruptured intracranial aneurysms. Early endovascular treatment even if not correlated to a good clinical outcome, may explain the low incidence of early rebleeding in our series, without being associated with a higher risk of intra-procedural rupture. Since the incidence of pre-treatment rebleedings within 12 hours was similar in patients treated between 12 and 48 hours, our data would not justify the hyper-early treatment of ruptured intracranial aneurysms. From our experience and according to data previously reported in literature the endovascular treatment of ruptured intracranial aneurysms should be performed within 24 hours.

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Arturo Consoli MD
Interventional Neuroradiology Unit Careggi
University Hospital Florence
Largo Brambilla
350134 Firenze, Italy
Tel.: +39 055 7947490
Fax: +39 055 7947087
E-mail: onemed21@gmail.com